

Remarks:

After entry of the amendment, claims 3-6, 11, 74-75 and 80-82 are pending.

Claims 16-24, 29, 35-39, 44, 48, 50, 55, 59, 61, 66-70, 72, 73, 76 and 91 have been cancelled without prejudice or disclaimer. Applicant retains the right to pursue the subject matter of these claims in future continuation or divisional applications.

In view of the cancellation of claim 76, the dependency of claim 80 has been amended

No issues of new matter should arise and entry of the amendment is respectfully requested.

A. Rejection under 35 U.S.C. §112, First Paragraph

Claims 5, 6, 11, 16-24, 29, 35-39, 44, 48, 50, 55, 59 and 61 are rejected under 35 USC § 112, first paragraph, as lacking enablement. Claims 5 and 6 pending after entry of the amendment.

Applicant respectfully traverses the rejection and respectfully submits that the claims satisfy the requirement under 35 U.S.C. § 112, first paragraph.

The Examiner asserts that there is no teaching in the prior art that the compounds of Formula IV and V are known for the treatment of hypertension. Applications respectfully submit that the parent compounds of Formula (IV) and (V) (i.e. the non-nitrosylated and/or nitrosated compound)) are the active hydroxyl metabolites of nebivolol. In support thereof, attached hereto as Appendix A, is the package insert for Nebilet tablets (i.e. tablets that contain 5 mg nebivolol hydrochloride). As stated on lines 1 -2 of the Section entitled "Pharmokinetics":

"Nebivolol can be given with or without meals with peak plasma concentrations occurring within 2 – 6 hours after dosing. It is extensively metabolized partly to **active hydroxyl metabolites.**"
(Emphasis added)"

As pointed out by the Examiner on page 2 of the Office Action dated June 16, 2005, the specification is enabled for the treatment of hypertension using the compounds of Formula I (i.e. the nitrosated and/or nitrosylated derivatives of nebivolol). Therefore the specification must also be enabled for its active metabolites i.e. the compounds of Formula (IV) and (V).

The Examiner asserts that the specification is not enabled for treating hypertension with the compounds of Formulas (I), (IV) and (V) in combination with other therapeutic agents. In

view thereof, and in order to further prosecution, claims 16-24, 29, 35-39, 44, 48, 50, 55, 59, 61 and 66-70, 72 and 73 have been cancelled.

In view of the above, Applicant respectfully submits that the claims satisfy the requirement under 35 U.S.C. § 112, first paragraph, and respectfully request that the rejection under this provision be withdrawn.

B. Rejection under 37 C.F.R. §112, second paragraph

Claims 48, 59, 76 and 91 are rejected under 37 C.F.R. §112, second paragraph, as being indefinite.

In view of the cancellation of claims 48, 59, 76 and 91 the rejection is now moot. Applicant respectfully submits that the claims satisfy the requirement under 35 U. S. C. §112, second paragraph, and respectfully request that the rejections under this provision be withdrawn.

C. Rejection under 35 U.S.C. §103

Claims 3-6, 11, 16-24, 29, 35-39, 44, 48, 50, 55, 59, 61, 66-70, 72-76, 80-82 and 91 are rejected under 35 U.S.C. § 103(a) as obvious over Van Lommen et al. (U.S. Patent No. 4,654,362), in view of Loscalzo et al. (U.S. Patent No. 6,635,273). After entry of the amendment, claims 3-6, 11, 74-75 and 80-82 are pending.

As previously pointed out by the Examiner, Van Lommen does not disclose or suggest the presently claimed **nebivolol compounds that comprise at least one NO and/or NO₂ group**, and does not provide any motivation or incentive to add at least one NO and/or NO₂ group to nebivolol.

Loscalzo teaches **methods** of treating vascular diseases due to nitric oxide insufficiency by administration of a nitrosated beta-adrenergic blocker. Nebivolol is listed in the laundry list of possible beta-adrenergic blocker that can be administered. Loscalzo **does not disclose** the presently claimed nitrosated and/or nitrosylated nebivolol compounds of Formula (I), (IV) or (V), nor does Loscalzo suggest or motivate one to make the nitrosated and/or nitrosylated nebivolol compounds of Formula (I), (IV) or (V) of the present invention. As pointed out by the Examiner from Loscalzo, it is not clear how to attach the –NO group or the –NO₂ group to the structure of nebivolol. There is absolutely no guidance in Loscalzo as to how to attach the –NO group or the –NO₂ group to nebivolol, where it is attached to nebivolol and how many –NO group or the –NO₂ group are attached to nebivolol. Hence Loscalzo taken alone does not render the claimed invention obvious. Additionally Loscalzo does not provide any motivation or

suggestion to modify Van Lommen to arrive at the claimed invention. In view thereof, Loscalzo in combination with Van Lommen does not motivate one to arrive at the present invention.

In view thereof, Applicant respectfully submits that the claims of the present invention are unobvious over the cited references, alone and in combination, and respectfully request the rejection under 35 U.S.C. §103(a) be withdrawn.

D. Second Rejection under 35 U.S.C. §112, Second Paragraph

Claims 17, 18, 19-21 and 22 are rejected under 35 USC § 112, second paragraph, as lacking enablement.

Applicant respectfully traverses the rejection and respectfully submits that the claims satisfy the requirement under 35 U.S.C. § 112, second paragraph. In view of the cancellation of claims 17, 18, 19-21 and 22 the rejection is now moot, and respectfully request that the rejections under this provision be withdrawn.

E. Conclusion

Applicant respectfully requests reconsideration and allowance of claims 3-6, 11, 74-75 and 80-82. The Examiner is encouraged to contact the undersigned concerning any questions about the present application.

Respectfully submitted,



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